DEPARTMENT OF HEALTH AND HUMAN SERVICES

95108d

Food and Drug Administration
Atlanta District Office

60 8th Street, N.E.
Atlanta, Georgia 30309

November 29, 2004

VIA FEDERAL EXPRESS

George Gunn, Global Head
Novartis Animal Health Services AG
Werk Rosental
Schwarzwaldallee 215
WRO-132.5.50
CH-4058 Basel
Switzerland

WARNING LETTER
(05-ATL-06)

Dear Mr. Gunn:

During the period of January 20 through January 23, 2004, an inspection was conducted at the headquarters of your veterinary pharmaceutical operations in the United States of America (USA), known as Novartis Animal Health US, Inc. (Novartis), which are located at 3200 Northline Avenue, Suite 300 in Greensboro, North Carolina. The inspection disclosed significant deviations from the adverse drug experience (ADE) reporting requirements of Section 512(l) of the Federal Food, Drug, and Cosmetic Act (the Act) and Title 21, Code of Federal Regulations (21 CFR), Sections (§§) 510.300 (effective prior to June 30, 2003) and 514.80 (effective on June 30, 2003). Upon the conclusion of the inspection on January 23, 2004, a Form FDA 483 - Inspectional Observations (FDA 483) was issued to and discussed with Dr. Guy L. Tebbit, Vice President, Regulatory Affairs. In addition, as noted below, a number of similar deviations have occurred since the FDA 483 was issued. For example, you sent a letter on September 21, 2004, submitting two late ADEs and describing corrective actions Novartis has taken as a result.

The primary purpose of the inspection was to determine Novartis' compliance with the ADE reporting requirements of the Act and its regulations. The inspection included, but was not limited to, a review of Novartis' ADE reports for lack of expected effectiveness (LOE) complaints concerning your heartworm prescription drug products Interceptor® and Sentinel® for all marketing years subsequent to their approval.

The Form FDA 1932 "Veterinary Adverse Drug Reaction, Lack of Effectiveness, Product Defect Report" (FDA 1932) is used to report ADEs and product/manufacturing defects. 21 CFR §§ 514.80(b)(1), (b)(2), and (b)(4)(iv). ADEs include, among other events, LOEs and ADEs occurring in humans from exposure during manufacture, testing, handling, or use. 21 CFR § 514.3.

The inspection disclosed significant deviations from the applicable requirements of the Act and regulations. Upon its conclusion on January 23, 2004, a Form FDA 483 - Inspectional Observations (FDA 483) was issued to and discussed with Dr. Guy L. Tebbit, Vice President, Regulatory Affairs. A copy of the FDA 483 is enclosed for your review.

We would like to point out to you that in item # 1 of the FDA 483 we made reference to Case # US200302009. Upon further review, we have determined that this incident was reported appropriately to the FDA and should not have been included in the FDA 483. We apologize for any confusion caused by this inadvertent error.

We acknowledge the receipt of several pieces of correspondence from Novartis containing responses to the inspectional observations found in the FDA 483. Your responses were dated as follows: February 4, 2004; February 25, 2004; an undated letter from Dr. Tebbit (possibly April 16, 2004); April 19, 2004; April 23, 2004; and June 3, 2004. We will address some of our concerns with those responses in the discussion that follows.

Based on our evaluation of the information obtained during the course of the inspection, the documentation related to Novartis' ADE reports submitted to FDA over the last six (6) years, and Novartis' written responses following the inspection, we have determined that your firm has failed to comply with the ADE reporting requirements of Section 512(l) of the Act and 21 CFR §§ 510.300 (effective prior to June 30, 2003) and 514.80 (effective on June 30, 2003).

The violations include, but are not limited to, the following areas:

Problems associated with your reporting practices of ADEs:

Novartis failed to submit timely and accurate information to the FDA regarding serious ADEs associated with the administration of its FDA approved animal drug product Deramaxx™ (Deracoxib), New Animal Drug Application (NADA) 141-203, during its first year of marketing.

An example of this type of deviation is the recording of the date sent to FDA (box 2b of the FDA 1932). Our inspection revealed significant discrepancies between what was written in box 2b of the FDA 1932 and the postmarked date of the submission and/or the date FDA received the submission. Some of Novartis' initial and follow-up ADE reports, including ones involving death, were postmarked and/or received by FDA

between 21 and 100 or more days after the date recorded in box 2b of the FDA 1932, indicating that the date recorded in box 2b is incorrect.

Another example is Case # US200302088, which was reported to Novartis on February 19, 2003 (as indicated in box 2a of the FDA 1932). The form indicates that it was sent to FDA on January 9, 2004, over 10 months after it was reported to Novartis. This information should have been reported to FDA in a timely manner, within 15 working days of receipt. Moreover, the report was not received by FDA until January 27, 2004, again indicating that the date recorded in box 2b was incorrect.

A third example is the revised submission for Case # US200207030, which was submitted with your response dated February 25, 2004. Our investigators reviewed the entire correspondence file between the owner of this animal and Novartis. The FDA 1932 submitted with your response fails to include specific details regarding the results of blood work performed on this dog on September 9, 2002 (a baseline) and further work performed in October 2002 and November 2002, which was transmitted to Novartis by the owner between November 2002 and January 2003, in violation of 21 CFR § 514.80(b)(2)(ii). This information should have been promptly reported to FDA within 15 working days of receipt.

Your written response dated February 25, 2004, included revised standard operating procedures (SOPs), which were supposed to address the observed deficiencies. The revised SOP 5.2 (Volume 1, page 650) does not identify how your firm will prevent incorrect information from being reported to FDA as was noted during the inspection.

Your written response dated April 23, 2004, indicates that Novartis has employed additional personnel for the receipt, investigation, and transmittal of ADE reports. The response further states that your firm has also involved corporate quality, compliance, and pharmacovigilance groups to assist in this process. But following your response FDA has continued to receive late ADE reports along with cover letters. For example, some of these letters were dated April 28, 2004; May 12, 2004; May 28, 2004; July 29, 2004; August 20, 2004; and September 21, 2004.

Problems associated with your reporting practices of ADEs related to experimental studies:

Your firm failed to submit timely information to the FDA regarding post-approval studies involving new animal drugs. Two specific failures were identified during the inspection.

The first one was the failure to submit information from completed pilot studies as part of the clinical experience in the annual Drug Experience Report (DER), as required by 21 CFR § 510.300(a)(1) (effective prior to June 30, 2003) and 514.80(b)(4)(iii) (effective on June 30, 2003). Our investigators identified over [redacted] pilot studies in your master study list. Dr. Tebbit stated that Novartis has never submitted information about their pilot studies as part of the annual DER, unless they are part of an Investigational New

Animal Drug Application (INADA) or a pivotal study.

The second one was the failure to submit serious, unexpected ADEs involving animals under study to the FDA within 15 working days of first receiving the information, as required by 21 CFR § 510.300(b)(2)(l) (effective prior to June 30, 2003) and 514.80(b)(2)(i) (effective on June 30, 2003).

One study involving Deramaxx™ (Deracoxib), NADA 141-203, in cats involved a late submission of ADEs. The experiment, which was completed in July 2003, involved 14 animal deaths and other serious ADEs. These ADEs were not reported to the FDA within the required 15 working days timeframe, but were reported only after the conclusion of the inspection of your facility, on February 24, 2004.

Although your submission dated February 24, 2004, indicates that it was Novartis' intent to disclose the safety information from the cat study, your firm failed to disclose this information from other studies found in the master study list.

For example, a protocol entitled "The Acute Safety Study of an Injectable Deracoxib (SD-6746) Formulation in Dogs" was submitted to the FDA under the INADA 010-865 on April 15, 2002. This was approximately three months after the master study list indicates the pilot study was completed. The study clinical data was not received by the FDA until October 2004.

FDA acknowledges that your firm has revised its SOPs and obtained principal investigator agreements to submit all 15-day ADEs in post approval studies as drug experiences. But your response does not clarify that you also understand that you must submit ADEs in the periodic drug experience report as clinical data, unless they were previously reported, as required by 21 CFR § 514.80(b)(4)(iv)(C).

Problems associated with your reporting practices of human exposure ADEs:

Clomicalm® (Clomipramine Hydrochloride), NADA 141-120, has the potential for human abuse and carries the following human warning statement on its label:

> ***Human Safety Relative to Possession, Handling and Administration:***
>
> ***"Not for use in humans. Keep out of reach of children. In case of accidental ingestion seek medical attention immediately. In children, accidental ingestion should be regarded as serious. There is no specific antidote for clomipramine. Overdose in humans causes anticholinergic effects including effects on the central nervous (e.g. convulsions) and cardiovascular (e.g. arrhythmias, tachycardia) systems. People with known***

hypersensitivity to clomipramine should administer the product with caution."

Our review of your submissions involving human adverse experience events for Clomicalm® since April 23, 2004, indicates that your firm should improve its reporting of follow-up information. All adverse drug events that are on the 15-day report must be promptly investigated and significant new information must be reported to FDA within 15 working days of receiving such information. 21 CFR § 514.80(b)(2)(ii). For example, significant new information would include instances where humans experienced any side effects from taking this drug.

Neither this letter nor the FDA 483 which was issued to and discussed with Dr. Tebbit is intended to be an all-inclusive list of deficiencies at your firm. It is your responsibility to ensure adherence to each requirement of the Act and its regulations.

The specific violations noted in this letter are serious and may be symptomatic of serious underlying problems.

You should take prompt action to correct these deficiencies. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions may include, but are not limited to, seizure and/or injunction. Federal agencies are advised of all Warning Letters about drugs so they may take this information into account when considering the award of contracts.

We request that you reply in writing within fifteen (15) working days of receipt of this letter describing the corrective actions you have implemented, or are planning to implement, to prevent a recurrence of the violations noted above. Please include copies of any available documentation demonstrating that corrections have been made. If corrective actions cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which the corrections will be completed.

Your written response and any pertinent documentation should be addressed to Philip S. Campbell, Compliance Officer, at the address noted in the letterhead.

Sincerely yours,

Barbara A. Ward
for Mary H. Woleske
District Director
Atlanta District

Enclosure